12877

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
D 2145 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/08570	01/09/2000	10/09/1999
Applicant		
EPIDAUROS BIOTECHNOLOGIE AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readble form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/08570

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C12P19/34 C12N9/02 C07K16/18 C12N15/53
A61K38/17 A61P35/00 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WESTLIND A ET AL.,: " Interindividual differences in hepatic expression of CYP3A4: Relationship to genetic polymorphism in the 5'-upstream regulatory region." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 259, 27 May 1999 (1999-05-27), page 201-205 XP000907112 the whole document ---	1-3,13, 14,19, 21,26-33
X	WO 99 13106 A (AXYS PHARM INC) 18 March 1999 (1999-03-18) the whole document --- -/--	1-9, 12-43

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2001	09. 5. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HASHIMOTO H. ET AL.,: "Gene structure of CYP3A4 an adult-specific form of cytochrome P450 in human livers and its transcriptional control" EUR. J. BIOCHEM., vol. 218, 1993, page 585-595 XP000910643 cited in the application the whole document	1-3
X	BEAUNE P.H. ET AL.,: "Isolation and sequence determination of a cDNA clone related to human cytochrom P-450 nifedipine oxidase" PROCEEDINS OF THE NATIONAL ACADEMY OF SCIENCES, USA, vol. 83, 1986, pages 8064-8068, XP000907192 cited in the application the whole document	1-3
A	WO 91 10745 A (IMP CANCER RES TECH) 25 July 1991 (1991-07-25) the whole document	1-3, 12-14, 25,27, 35,36, 38,40,41
A	EP 0 759 476 A (OTSUKA PHARMA CO LTD) 26 February 1997 (1997-02-26) the whole document	1-3, 12-14, 25,27, 35,36, 38,40,41
P,X	WO 00 24926 A (LABUDA DAMIAN ;SINNETT DANIEL (CA); HOPITAL SAINTE JUSTINE (CA)) 4 May 2000 (2000-05-04) page 3, line 1 -page 4, line 34 page 5, line 21-32; claims 8-13; example 3	1-3,13, 14,19, 26-33, 36-39
T	SATA F ET AL.,: "CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: Evidence for an allelic variant with altered catalytic activity" CLINICAL PHARMACOLOGY & THERAPEUTICS, vol. 67, January 2000 (2000-01), page 48-56 XP000910497 cited in the application the whole document	1-3,13, 14,19, 26-33, 36-39

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	NCBI protein and nucleotide databasases. 15-11-2000 AC= AAG32290. CYTOCHROME P450 POLYPEPTIDE 4; CYP3A4. Homo sapiens (Human). Gellner et al., "Genomic organization of the human CYP3A locus: identification of a new, inducible CYP3A gene expressed in the liver, testes and prostate." (unpublished) XP002158367 abstract ----	1-43

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT 00/08570

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9913106 A	18-03-1999	AU 9128798 A	29-03-1999
		EP 1012340 A	28-06-2000
WO 9110745 A	25-07-1991	AT 140488 T	15-08-1996
		AU 642705 B	28-10-1993
		AU 7179191 A	05-08-1991
		CA 2071636 A	19-07-1991
		DE 69120936 D	22-08-1996
		DE 69120936 T	20-02-1997
		EP 0511262 A	04-11-1992
		GB 2256271 A,B	02-12-1992
		JP 5503845 T	24-06-1993
		US 5981174 A	09-11-1999
EP 0759476 A	26-02-1997	JP 7298900 A	14-11-1995
		CA 2189638 A	16-11-1995
		CN 1151763 A	11-06-1997
		WO 9530772 A	16-11-1995
WO 0024926 A	04-05-2000	US 6183963 B	06-02-2001
		AU 6322299 A	15-05-2000

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M1 (having a nucleotide substitution at position 6004) and a molecular variant of the cytochrome CYP3A7 (having a nucleotide substitution at position 1229), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4 or CYP3A7.

2. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M2 (having a nucleotide substitution at position 13908), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

3. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M3 (having a nucleotide substitution at position 14292), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

4. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M4 (having a nucleotide substitution at position 14304), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

5. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M5 (having a nucleotide substitution at position 21867), its corresponding nucleotide and protein sequences; vectors;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

6. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M6 (having a nucleotide substitution at position 21896), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

7. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M7 (having a nucleotide substitution at position 22026), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

8. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M8 (having a nucleotide substitution at position 23172), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

9. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M10 (having a nucleotide substitution at position 14323), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M11 (having a nucleotide substitution at position 14329), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

11. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M12 (having a nucleotide substitution at position 14357), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

12. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M13 (having a nucleotide substitution at position 15753), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

13. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M14 (having a nucleotide substitution at position 20230), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

14. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M15 (having a nucleotide substitution at position 21868), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

15. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M16 (having a nucleotide substitution at position 22041), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

16. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M17 (having a nucleotide substitution at position 23081), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

17. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M18 (having a nucleotide substitution at position 25925), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

18. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M19 (having a nucleotide substitution at position 25958), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,33,34,37

Present claims 1 and 37 relate to an extremely large number of polynucelotide sequence of which only a small fraction could be unambiguously allocated to the CYP3A4 or CYP3A7 variants. In fact, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those sequences succesfully allocated with the help of tables 1-4.

Claims 33 and 34 refer to an inhibitor identified or obtainable by screening compounds able to displace the protein of claim 9 when is bound to a CYP3A4 (or CYP3A7); or contacting such protein with compounds capable of providing a detectable signal in response to drug metabolization. No such compounds are defined in the application. In consequence the scope of said claim is ambigous and vague, and its subject-matter is not sufficiently disclosed and supported (Art. 83 and 84 EPC).
Therefore, no search can be carried out for such speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/08570

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 28 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1,33,34,37
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-43 all partially

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.